Value of routine echocardiography in the management of stroke

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Cite as: *CMAJ* 2019 August 6;191:E853-9. doi: 10.1503/cmaj.190111

ABSTRACT

BACKGROUND: Transthoracic echocardiography is routinely performed in patients with stroke or transient ischemic attack (TIA) to help plan secondary stroke management, but recent data evaluating its usefulness in this context are lacking. We sought to evaluate the value of echocardiography for identifying clinically actionable findings for secondary stroke prevention.

METHODS: We conducted a multicentre cohort study of patients admitted to hospital with stroke or TIA between 2010 and 2015 at 2 academic hospitals in Toronto, Ontario, Canada. Clinically actionable echocardiographic findings for secondary stroke prevention included cardiac thrombus, patent foramen ovale, atrial myxoma or valvular vegetation. We identified patient characteristics associated with clinically actionable findings using logistic regression.

RESULTS: Of the 1862 patients with stroke or TIA we identified, 1272 (68%) had at least 1 echocardiogram. Nearly all echocardiograms were transthoracic; 1097 (86%) were normal, 1 (0.08%) had an atrial myxoma, 2 (0.2%) had a valvular vegetation, 11 (0.9%) had a cardiac thrombus and 66 (5.2%) had a PFO. Patent foramen ovale was less likely among patients older than 60 years (adjusted odds ratio [OR] 0.34, 95% confidence interval [CI] 0.20–0.57), with prior stroke or TIA (adjusted OR 0.31, 95% CI 0.09–0.76) or with dyslipidemia (adjusted OR 0.39, 95% CI 0.15–0.84). Among the 130 patients with cryptogenic stroke who had an echocardiogram (n = 110), a PFO was detected in 19 (17%) on transthoracic echocardiogram.

INTERPRETATION: Most patients with stroke or TIA had a normal echocardiogram, with few having clinically actionable findings for secondary stroke prevention. Clinically actionable findings, specifically PFO, were more common in patients with cryptogenic stroke.

Stroke is the third leading cause of death in high-income countries, and accounts for substantial morbidity in those who survive.[1] Ischemic stroke is primarily due to a thrombotic or embolic event, and emboli frequently originate in the heart.[2] Transthoracic echocardiography can sometimes diagnose cardiac sources of embolism, such as atrial or ventricular thrombus,[3–5] and these generally require anticoagulation. Transthoracic echocardiography can also identify other causes of stroke that may require intervention, such as atrial abnormalities (e.g., patent foramen ovale, atrial myxoma)[6–8] or infective endocarditis.

Transthoracic echocardiography is often recommended to plan secondary stroke management, but it is unclear how often this test provides clinically actionable findings.[4,9] Previous studies provide a range of conflicting estimates for how often transthoracic echocardiography might affect patient management because of changing opinions on what pathology is considered clinically relevant.[10,11] For example, dilated cardiomyopathy is no longer an indication for anticoagulation among patients with stroke.[12] Other findings previously considered to be incidental, such as patent foramen ovale, are now clinically actionable among patients with cryptogenic stroke.[6–8] Current stroke clinical practice guidelines do not reflect these nuanced data, making it challenging for physicians to know which patients should have transthoracic echocardiography after an ischemic stroke.[9,13,14] Furthermore, data that are both comprehensive and recent are lacking to further understanding of how often patients in routine care with stroke will have echocardiographic findings that are clinically actionable.

Choosing Wisely[15] advocates against routine low-value care that is unlikely to improve patient care or is likely to cause harm. Transthoracic echocardiography is unlikely to cause direct patient harm but may cause indirect harm; for example, where incidental findings lead to invasive testing (i.e., transesophageal echocardiography) and expose patients to additional risks. Awaiting transthoracic echocardiography can also

delay timely access to stroke rehabilitation, which is an integral part of stroke care.[16,17] The objective of our study was to quantify how often clinically actionable findings were detected on echocardiogram for secondary stroke prevention in patients with stroke, and also specifically cryptogenic stroke, and to identify situations in which echocardiography might be of high or low value.

Methods

Study setting

We conducted a cohort study of patients admitted to hospital with ischemic stroke or transient ischemic attack (TIA) at St. Michael's Hospital or Sunnybrook Health Sciences Centre, 2 teaching hospitals in Toronto, Ontario, Canada, between Apr. 1, 2010, and Mar. 31, 2015. Hospital services are publicly insured for residents of Ontario, and the 2 participating hospitals serve a diverse urban population from a variety of socioeconomic backgrounds.

Data source

Data were collected from the General Medicine Inpatient Initiative (GEMINI) database.[18] It contains data for all patients admitted to hospital under general internal medicine at several hospitals in Toronto (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190111/-/DC1). We included data from 2 hospitals to which patients with stroke are routinely admitted under general internal medicine. Two physicians (I.F. and S.H.) were trained to manually extract the following patient-level data from the medical record: history of prior stroke or TIA, previous diagnosis of atrial fibrillation, medications before hospital admission, discharge medications, postdischarge referrals and echocardiogram findings. Echocardiogram results were extracted from finalized reports produced by a cardiologist trained in echocardiography. For patients who had more than 1 echocardiogram during their hospital stay, we extracted the results of the first, as tests performed later in the stay may not necessarily have been attributable to their presenting stroke or TIA. For patients with cryptogenic stroke, we reviewed both transthoracic and transesophageal echocardiography results for all patients who had both. We performed duplicate extraction on a random 15% sample of our study population to assess interrater reliability. Discrepant findings were adjudicated by a third physician (N.G.).

Study population

We identified patients with a most responsible discharge diagnosis of ischemic stroke using the *International Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) diagnostic criteria codes for ischemic stroke (Appendix 1). These codes have been previously validated at other Canadian academic teaching hospitals and have a positive predictive value above 89%.[19] For patients with more than 1 stroke during our study's time frame, we included only the results from their first admission for stroke. Patients who received tissue plasminogen activator were excluded from our study as these patients are admitted to the intensive care unit and then admitted to a neurology service, and thus not consistently captured in the GEMINI database. All other patients with a most responsible discharge diagnosis of ischemic stroke or TIA were included.

To identify patients with cryptogenic stroke, we applied the exclusion criteria as used in the recently published clinical trials of patent foramen ovale closure (Appendix 1).[6–8] Patients who were initially considered to have a stroke but were subsequently given a different diagnosis would not be captured in our cohort if their most responsible discharge diagnosis was not stroke or TIA. Additional chart review was performed to quantify how often this occurred in GEMINI (Appendix 1).

Study outcomes

The primary outcome was the proportion of patients with an echocardiogram with clinically actionable findings for secondary stroke prevention. These were defined using the American Heart Association stroke guideline.[20] Clinically actionable findings for secondary stroke prevention included atrial or ventricular thrombus, patent foramen ovale, atrial myxoma or valvular vegetation. We also quantified how often these findings directly led to change in clinical management. As a secondary outcome, we quantified the proportion of other echocardiographic findings that could affect clinical management in other ways (e.g., left ventricular fraction < 35%).

Statistical analysis

Descriptive statistics were used to characterize patient-level characteristics, time from hospital admission to echocardiography, and total length of hospital stay. Categorical data were compared with a χ^2 test; continuous data were compared with either the Student *t* test with unequal variance for means or the Mann–Whitney *U* test for medians.

We performed logistic regression to examine the association between patient characteristics and detection of cardiac thrombus or patent foramen ovale, as they are the most common management-changing echocardiographic findings. Because thrombus and patent foramen ovale have different risk factors, we tested different patient characteristics for each abnormality. We first conducted an unadjusted analysis and then built a multivariable logistic regression model and selected patient characteristics to be included based on prior literature on potential risk factors for patent foramen ovale.[21–23] We did not build a multivariable model for cardiac thrombus because there were too few events. Differences in length of stay for patients who received an echocardiogram compared with those who did not were modelled using quantile regression as length of stay was not normally distributed (quantreg package, available at https://cran.r-project.org/web/packages/quantreg/quantreg.pdf). Manually extracted data were analyzed for consistency using Cohen's κ (Appendix 1). All statistical analyses were performed using R version 3.2.

Ethics approval

This study was approved by the research ethics boards of St. Michael's Hospital and Sunnybrook Health Sciences Centre.

Results

Study cohort

Between Apr. 1, 2010, and Mar. 31, 2015, there were 2014 patients with a discharge diagnosis of stroke or TIA (Appendix 1). We excluded 114 patients because they were being readmitted after their initial stroke or TIA, 29 patients who did not have an Ontario health care number and 9 patients who did not have a discharge summary. Among the remaining 1862 patients, about half were women, their average age was about 74 years, 65% had hypertension and 23% had atrial fibrillation (Table 1). Echocardiography was performed in 1272 (68%) patients. Patients receiving an echocardiogram were more often men and were on average 5 years younger than those not receiving an echocardiogram. Of the patients who received an echocardiogram, 1219 (96%) had 1 transthoracic echocardiogram and no transesophageal echocardiogram, 19 (2%) had more than 1 transthoracic echocardiogram and no transesophageal echocardiogram, 29 (2%) had 1 transthoracic echocardiogram and 1 transesophageal echocardiogram, 3 (0.2%) had more than 1 transthoracic echocardiogram and 1 transesophageal echocardiogram, and 2 (0.2%) had no transthoracic echocardiogram and 1 transesophageal echocardiogram.

In the subset of 130 patients with presumed cryptogenic stroke (Appendix 1), the mean age of included patients was 50 years, 37% were female, and many had no traditional risk factors for stroke (Supplementary Table 1, Appendix 1). Of these patients, 109 (84%) had a transthoracic echocardiogram, 11 (9%) had a transesophageal echocardiogram in addition to a transthoracic echocardiogram, and 1 (1%) had a transesophageal echocardiogram without a transthoracic echocardiogram.

Table 1: Baseline characteristics of patients with stroke or transient ischemic attack

Characteristic	No. (%)* of patients with echocardiography *n* = 1272	No. (%)* of patients without echocardiography *n* = 590
Age, yr, mean ± SD	72.5 ± 14.1	77.4 ± 14.0
Sex, male	670 (53)	264 (45)
Atrial fibrillation	307 (24)	126 (21)
Hypertension	824 (65)	374 (63)
Dyslipidemia	281 (22)	123 (21)
Prior stroke or TIA	243 (19)	139 (24)
Diabetes mellitus	340 (27)	149 (25)
Coronary artery disease	128 (10)	60 (10)
Heart failure	73 (6)	26 (4)
Antiplatelet use	396 (31)	215 (36)
Anticoagulant use	141 (11)	75 (13)

Note: SD = standard deviation, TIA = transient ischemic attack.
*Unless stated otherwise.

Echocardiographic findings

Overall, most patients (*n* = 1097, 86%) had a normal echocardiogram, 1 patient (0.08%) had an atrial myxoma, 2 patients (0.2%) had a valvular vegetation, 11 patients (0.9%) had a cardiac thrombus and 66 patients (5.2%) had a patent foramen ovale (Table 2).

Of the 66 (5.2%) patients who had a patent foramen ovale, none were referred for closure. Of the 11 (0.9%) patients who had a cardiac thrombus, 5 already had an indication for anticoagulation (most often atrial fibrillation). For the remaining 6 patients, 5 were

Table 2: Echocardiography results in patients with stroke or transient ischemic attack

Characteristic	No. (%) of patients with echocardiography *n* = 1272	No. (%) of patients with non-cryptogenic stroke *n* = 1162	No. (%) of patients with cryptogenic stroke *n* = 110
Normal	1097 (86)	1016 (87)	81 (74)
Patent foramen ovale	66 (5)	47 (4)	19 (17)
Ejection fraction < 35%	38 (3)	35 (3)	3 (3)
Dilated cardiomyopathy	27 (2)	25 (2)	2 (2)
Left ventricular aneurysm	20 (2)	15 (1)	5 (5)
Bioprosthetic valve	18 (1)	18 (2)	0 (0)
Mitral stenosis	16 (1)	16 (1)	0 (0)
Thrombus	11 (0.9)	11 (1)	0 (0)
Restricted cardiomyopathy	2 (0.2)	2 (0.2)	0 (0)
Mechanical valve	10 (0.8)	8 (0.7)	2 (2)
Vegetation	2 (0.2)	2 (0.2)	0 (0)
Myxoma	1 (0.1)	1 (0.1)	0 (0)

*The echocardiography findings in this table are based on the first echocardiogram performed in hospital, which was most often (> 99%) a transthoracic echocardiogram. Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190111/-/DC1) provides additional details for the patients with cryptogenic stroke who had results of both the transthoracic echocardiogram and transesophageal echocardiogram reviewed.

Table 3: Characteristics of patients with a patent foramen ovale (PFO), thrombus, or no PFO or thrombus

Characteristic	No. (%)* of patients with no PFO or thrombus *n* = 1195	No. (%)* of patients with PFO *n* = 66	No. (%)* of patients with thrombus *n* = 11
Sex, male	624 (52.2)	36 (54.5)	10 (90.9)
Age, yr (median, IQR)	75 (64–84)	63 (49–80)	67 (62–68)
Atrial fibrillation	294 (24.6)	9 (13.6)	4 (36.4)
Hypertension	785 (65.7)	34 (51.5)	5 (45.5)
Dyslipidemia	271 (22.7)	6 (9.1)	4 (36.4)
Previous stroke or TIA	237 (19.8)	4 (6.1)	2 (18.2)
Diabetes mellitus	323 (27.0)	13 (19.7)	4 (36.4)
Coronary artery disease	120 (10.0)	4 (6.1)	4 (36.4)
Heart failure	68 (5.7)	2 (3.0)	3 (27.3)

Note: IQR = interquartile range, PFO = patent foramen ovale, TIA = transient ischemic attack.
*Unless stated otherwise.

Table 4: Unadjusted logistic regression model of factors associated with cardiac thrombus*

Characteristic	No. (%) of patients with no thrombus *n* = 1261	No. (%) of patients with thrombus *n* = 11	Unadjusted OR (95% CI)
Atrial fibrillation	303 (24.0)	4 (36.4)	1.81 (0.47–6.02)
Sex, male	660 (52.3)	10 (90.9)	9.11 (1.74–167.37)
Age > 60 yr	1006 (79.8)	8 (72.7)	0.68 (0.19–3.10)
Hypertension	819 (64.9)	5 (45.5)	0.45 (0.13–1.50)
Dyslipidemia	277 (22.0)	4 (36.4)	2.03 (0.53–6.77)
Diabetes mellitus	336 (26.6)	4 (36.4)	1.57 (0.41–5.24)
Prior stroke or TIA	241 (19.1)	2 (18.2)	0.94 (0.14–3.68)
Heart failure	70 (5.6)	3 (27.3)	6.38 (1.38–22.60)
Coronary artery disease	124 (9.8)	4 (36.4)	5.24 (1.36–17.60)

Note: CI = confidence interval, OR = odds ratio, TIA = transient ischemic attack.
*A multivariable model was not performed for cardiac thrombus because there were too few patients with cardiac thrombus and doing so would result in overfitting.

newly started on anticoagulation. The 2 (0.2%) patients who were given a diagnosis of valvular vegetation were started on antibiotics. The single patient with an atrial myxoma was managed conservatively. In terms of other pathology detected on echocardiogram, 1.3% (n = 16) of patients had mitral stenosis and 3.0% (n = 38) had reduced left ventricular ejection fraction (Table 2).

In the subset of 110 patients with cryptogenic stroke who had echocardiography, 21 (19%) had a patent foramen ovale (p < 0.001 v. patients with non-cryptogenic stroke). Specifically, 17 were detected on transthoracic echocardiogram and 4 were detected on transesophageal echocardiogram (2 of which were also seen on transthoracic echocardiogram) (Table 2). The size of the foramen was provided for 5 patients. Four of the patients had a small and 1 patient had a moderate-sized lesion.

Predictors of thrombus and patent foramen ovale

The characteristics of patients with a cardiac thrombus or patent foramen ovale detected on echocardiography are described in Table 3. Patients with neither a thrombus nor a patent foramen ovale tended to be older (median age 75 yr) and two-thirds had a history of hypertension. Factors associated with cardiac thrombus were male sex, heart failure and coronary artery disease, among others (Table 4).

In a multivariable logistic regression model assessing the odds of detecting patent foramen ovale on echocardiogram, the presence of any of the following variables decreased the odds of patent foramen ovale: age older than 60 years (adjusted odds ratio [OR] 0.34, 95% confidence interval [CI] 0.20–0.57), presence of dyslipidemia (adjusted OR 0.39, 95% CI 0.15–0.84), or history of prior stroke or TIA (adjusted OR 0.31, 95% CI 0.09–0.76) (Table 5).

Table 5: Logistic regression model of factors associated with patent foramen ovale*

Characteristic	No. (%) of patients with no PFO *n* = 1206	No. (%) of patients with PFO *n* = 66	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Atrial fibrillation	298 (24.7)	9 (13.6)	0.48 (0.22–0.94)	NA
Sex, male	634 (52.6)	36 (54.5)	1.08 (0.66–1.79)	0.91 (0.54–1.53)
Age > 60 yr	977 (81.0)	37 (56.1)	0.30 (0.18–0.50)	0.34 (0.20–0.57)
Hypertension	790 (65.5)	34 (51.5)	0.56 (0.34–0.92)	0.77 (0.45–1.30)
Dyslipidemia	275 (22.8)	6 (9.1)	0.34 (0.13–0.73)	0.39 (0.15–0.84)
Diabetes mellitus	327 (27.1)	13 (19.7)	0.66 (0.34–1.19)	0.77 (0.39–1.42)
Prior stroke or TIA	239 (19.8)	4 (6.1)	0.26 (0.08–0.64)	0.31 (0.09–0.76)
Heart failure	71 (5.9)	2 (3.0)	0.50 (0.08–1.64)	NA
Coronary artery disease	124 (10.3)	4 (6.1)	0.56 (0.17–1.39)	NA

Note: CI = confidence interval, NA = not applicable, OR = odds ratio, PFO = patent foramen ovale, TIA = transient ischemic attack.
*We did not include atrial fibrillation, heart failure or coronary artery disease in our final model to avoid model overfitting and based on prior literature of risk factors for PFO.

Length of stay in hospital

The median time from hospital admission to echocardiography was 2.0 days (interquartile range [IQR] 1.0–3.4). Patients who had an echocardiogram had a median length of stay of 6.4 days (IQR 3.7–11.5), while patients who did not have an echocardiogram had a median length of stay of 3.3 days (IQR 1.8–6.6). After adjusting for baseline differences, patients who had an echocardiogram had a median length of stay that was about 3 days longer (3.01 d, 95% CI 2.58–3.44) than those who did not (Appendix 1).

Interpretation

In this multicentre cohort study of nearly 2000 patients who received a diagnosis of ischemic stroke or TIA, 68% had an echocardiogram (most often a transthoracic echocardiogram), and the results were normal 86% of the time. Overall, the 2 most common clinically actionable findings for secondary stroke prevention were cardiac thrombus and patent foramen ovale. Among patients with cryptogenic stroke, the prevalence of patent foramen ovale on echocardiography was more than 3 times higher than patients without cryptogenic stroke.

Previous studies have provided a wide range of estimates (2%–37%) for how often "clinically relevant" findings are detected on echocardiogram for patients with an ischemic stroke.[10–12,22] The wide range is partially related to changing criteria for what is considered clinically relevant. For example, 1 study published in 2003, of 853 patients with stroke, found on transthoracic echocardiogram that nearly 20% had dilated cardiomyopathy.[12] Based on the dilated cardiomyopathy, anticoagulation was considered to be beneficial, but this is no longer recommended in clinical practice guidelines.[14] As practice patterns change, updated data are necessary to re-evaluate the utility of echocardiography. After these data are available, there can be lags in changing clinical patterns until practice guidelines are updated.

Our study is one of the largest and provides some of the most up-to-date data on the utility of echocardiography for patients with stroke or TIA, and can help inform clinical practice guidelines. We found that most patients had a normal transthoracic echocardiogram, and only a small subset had clinically actionable findings for secondary stroke prevention. Patients with neither a cardiac thrombus nor a patent foramen ovale tended to be older and had a higher prevalence of hypertension, 2 of the strongest risk factors for ischemic stroke. Cardiac thrombus was associated with male sex and cardiac disease; younger patients without traditional stroke risk factors were more likely to have a patent foramen ovale. Taken together, these data can help clinicians gauge the urgency and utility of performing transthoracic echocardiography. Decision-making about whether transthoracic echocardiography must be performed in hospital can have important effects on length of hospital stay (and time to stroke rehabilitation), particularly where the procedure is not immediately available 7 days a week. The results of our study help provide an estimate for how the length of stay can potentially be affected for patients awaiting transthoracic echocardiography.

Previous studies from Canada indicate that about 70% of patients with stroke will have a transthoracic echocardiogram,[16] which is similar to our results. In contrast, 80%–90% of US patients with stroke will undergo transthoracic echocardiography.[11,24] The high rates of ordering might be explained, in part, by guidelines that do not provide specific indications for when transthoracic echocardiography should, and should not, be ordered.[13,25,26] A commonly held belief that transthoracic cardiography is part of a "routine stroke work-up,"[12] which continues to be taught in medical school, published in clinical textbooks[27] and practised in hospitals may explain high rates of ordering of this test.[28] It remains unclear what recommendations will be provided in the 2018 American Stroke Association Guidelines, in which multiple sections were recently redacted.[29]

A recent clinical practice guideline strongly recommends patent foramen ovale closure for patients with cryptogenic stroke,[30,31] but until 2018 patent foramen ovale was considered to be an incidental finding,[32] which likely explains why none of the patients with patent foramen ovale in our study were referred for closure of the defect. About 19% of patients with cryptogenic stroke in our study had a patent foramen ovale. In comparison, another study of patients with cryptogenic stroke, in which all patients had a transthoracic echocardiogram, reported the prevalence of patent foramen ovale at closer to 40%.[32] We might be underestimating the prevalence, as in our study not all patients had a transthoracic echocardiogram. Furthermore, a recent meta-analysis of prospective studies that compared the utility of transthoracic to transesophageal echocardiography to detect patent foramen ovale in patients with cryptogenic stroke determined the sensitivity of transthoracic echocardiography to be 45% (95% CI 31%–60%).[33] Similar results were observed in a meta-analysis of studies in which transthoracic echocardiography included a bubble study.[34] It is unknown what percentage of patients in routine care with cryptogenic stroke should ideally have a transesophageal echocardiogram, which is nearly 100% sensitive for patent foramen ovale, or when it should occur.[33,34] In the clinical trials for closure of patent foramen ovale, patients had both a transthoracic and a transesophageal echocardiogram and the defect was typically closed about 4 months after their stroke.[6–8] In our study, about 9% of patients with cryptogenic stroke had a transesophageal echocardiogram. These numbers may indicate the need for knowledge translation so that transesophageal echocardiography is considered for patients with cryptogenic stroke.

Limitations

First, we did not include patients who received tissue plasminogen activator, and thus our results do not apply to this patient population. In Canada, 8% of patients with ischemic stroke receive tissue plasminogen activator.[35] Second, our study included only patients admitted to hospital with stroke or TIA, and thus we may have overestimated the prevalence of echocardiographic abnormalities because patients in hospital might have a higher burden of comorbid conditions or more severe stroke compared with patients managed as outpatients.[36] Third, we identified patients with stroke or TIA by their most responsible discharge diagnosis. Although the diagnostic codes we used have been validated in other Canadian hospitals,[19,37] we may have missed patients who presented with stroke-like symptoms but were subsequently given a different diagnosis. To account for this, we reviewed all patients with an initial diagnosis of stroke who subsequently had a different most responsible discharge diagnosis, and doing so did not identify any patients with patent foramen ovale or cardiac thrombus who were "missed" (Appendix 1).

Conclusion

In our multicentre cohort study, we found that echocardiograms were most often normal for patients with stroke or TIA. In contrast, clinically actionable findings for secondary stroke prevention were more common in patients with cryptogenic stroke. Within this patient population, the importance of ruling out a patent foramen ovale has taken on new importance, as closure of the defect reduces the risk of subsequent stroke by more than 50%. The decision to pursue inpatient versus outpatient transthoracic echocardiography testing will depend on an individual patient's pretest probability, and our study provides timely data to aid in this estimation.

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Competing interests: Amol Verma and Fahad Razak report that they are part-time employee of Health Quality Ontario, as the Provincial Clinical Leads for Quality Improvement in General Internal Medicine. No other competing interests were declared.

This article has been peer reviewed.

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Contributors: All of the authors contributed to the conception and design of the work. Nicola Goldberg and Sagar Rohailla contributed to the acquisition of data. Michael Fralick, Nicola Goldberg, Matthew Burke, Fahad Razak, Amol Verma, Yishan Guo and Sagar Rohailla contributed to the analysis and interpretation of data. Michael Fralick, Nicola Goldberg, Yishan Guo carried out the statistical analysis. Mike Fralick and Nicola Goldberg drafted the manuscript. All authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Michael Fralick and Nicola Goldberg were joint primary authors. Fahad Razak and Amol Verma were joint senior authors.

Funding: This study was funded by Green Shield Canada Foundation and the Division of General Internal Medicine at the University of Toronto. Michael Fralick, Lauren Lapointe-Shaw and Amol Verma received funding from the Eliot Phillipson Clinician-Scientist Training Program at the University of Toronto. Michael Fralick received funding from the Clinician Investigator Program at the University of Toronto, and from The Detweiler Travelling Fellowship, funded by the Royal College of Physicians and Surgeons of Canada. Fahad Razak is supported by an award from the Mak Pak Chiu and Mak-Soo Lai Hing Chair in General Internal Medicine, University of Toronto.

Data sharing: The authors do not intend to share the data.

Acknowledgements: The authors thank Ismail Fakir and Shahina Haque for their help with data extraction and Hae Young Jung for his help with data analysis.

Accepted: June 14, 2019

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